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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,549	04/10/2001	James T. English	UMO 1521.1	8198

321 7590 07/25/2005

SENNIGER POWERS LEAVITT AND ROEDEL  
ONE METROPOLITAN SQUARE  
16TH FLOOR  
ST LOUIS, MO 63102

EXAMINER
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WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/829,549

**Applicant(s)**

ENGLISH ET AL.

**Examiner**

T. D. Wessendorf

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-9 and 32-51 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 32-51 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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**DETAILED ACTION**

***Status of Claims***

Claims 1-9 and 32-51 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections - 35 USC § 103***

Claims 1-4, 6-9, 32-34, 37-43, 45-47 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gough et al (Jrnl. Of Immunological Methods, 1999) in view of Kodacek et al (US 20010029024) and Petrenko et al (Protein Engineering) for reasons advanced in the last Office action of 2/9/2005.

***Response to Arguments***

Applicants recognize that Gough et al. describe identification of antibodies specific for surface-exposed epitopes on germlings of certain species of Phytophthora to be used for production of immunological probes and scFv antibodies which interfere with the infection process. Applicants argue that Gough et al. does not disclose phage display of a random peptide library or the selection of non-immunoglobulin peptides that bind epitopes on the surface of fungus. Gough et al. use only scFv antibody fragments in their disclosed phage display methods. Gough et al. report no problems associated with using antibody fragments in the disclosed phage display methodology

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for the purposes they pursued. Gough et al. do not suggest using peptides rather than antibody fragments in the disclosed methods. In fact, substituting peptides for antibody fragments in the method of Gough et al. would be unproductive in that Gough et al. seek to identify antibodies and not mere peptides. As illustration, Gough et al. states that "it remains an important goal to develop non- macromolecular species that retain the favorable molecular recognition characteristics of antibodies, but can be identified quickly and easily and synthesized in large amounts. Gough et al. state "the isolation of other scFvs (antibody fragments) specifically directed against the native conformation of surface- accessible antigens may well provide new tools to probe and manipulate pathogenicity."

To accomplish the objectives of Gough et al. (i.e., to isolate antibodies to surface antigens for use as immunological probes), one skilled in the art could not modify the disclosed methods so as to substitute random peptides (i.e., non-immunological) for scFvs.

In response, the suggested teachings of Gough of non-macromolecular species (i.e., fragments) that retain the recognition characteristics of antibodies like small molecule peptides mimics, would suggest the claimed peptide. Although,

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the claim recites a non-Ig peptide, which appropriately is not a macromolecule, as Ig, however, the function or characteristic of Ig is retained. In essence these peptides are antibodies mimics, as it is smaller recognition sequence site for an antigen, as the fungus. Gough suggestion of the strategy applied to their antibody has been based from the strategy achieved in peptide would lead one having ordinary skill in the art to a peptide. Gough at page 98, paragraph bridging cols. one and two states "the strategy described here for the isolation of antibodies against surface targets employs a phage-displayed single-chain fv..library in combination with affinity selection against whole organisms.....This rationale has been successfully applied to the selection of phage-displayed peptides that bind to the surface..." (Underlining provided.)

Applicants state that Kodacek et al. describe an assay to identify phage displayed specialized "pincer" peptides with high binding affinity for a single target peptide. Applicants state that the specialized approach of Kodacek facilitated identification of peptide-peptide interactions that were too unstable when either antibodies or simple peptides were displayed on the phage. Applicants argue that Kodacek and Gough cannot be combined without violating the objection of either reference. Applicants state that Gough represent mutually

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exclusive domains and any suggestion of substitution of the specialized peptides of Kodacek would not work.

In reply, Kodacek at [0129] discloses that the pincher peptide is one of the many ways by which the simple peptide can be modified, if one wishes to generate very high affinity epitope-binding molecules. That is the argued pincher peptide is a modified peptide that can additionally be tested in addition to the non-modified (simple) peptide.

Applicants argue that Kodacek also disclose similar disadvantages of peptides i.e., peptides or peptide epitopes in proteins are difficult target for molecular recognition studies in aqueous solution.

In reply, it appears from the above citation from Kodacek that the peptides relate to peptide epitopes embedded in proteins and not peptides per se, i.e., not in a protein.

Applicants further argue that Kodacek also say that "advances in single chain antibody libraries of phage promise to speed up this process." 'Thus, disadvantages of antibody usage are suggested to be minimized by the phage display methodology. No such claim was made for peptides. Rather, Kodacek disclose that previous efforts of the inventors to identify small molecular weight peptides that bound to surface epitopes by

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employing well-established methods of phage display failed completely.

In response, applicants appear to have taken out of context Kodacek's disclosure. Kodacek at [0038] states "the overall goal of this project was to develop a general method for the discovery of relatively low molecular weight EBMs that can be chemically synthesized (i.e., they are not macromolecules such as antibodies, other types of proteins, or nucleic acids). Thus, the inventor initiated an effort to isolate heteromeric complexes comprised of small peptides, even smaller than leucine zippers that could be employed as EBMs. As stated above, a priori, it was not clear how feasible this endeavor would be. Stable, specific complexes between naturally occurring peptides of less than 25-30 residues are essentially unknown, although complexes between small peptides and large proteins are very common. This is probably because macromolecular proteins have cavities into which a peptide can insert, thereby shielding many of the interactions from competition by solvent water. This kind of shielding is not possible for complexes between small peptides. Additionally, most peptides do not adopt stable secondary or tertiary structures, leading to the expectation that the entropic cost of forming a complex between small peptides would be much higher than binding of a peptide to a

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structurally well-defined protein. These very reasonable *biases* have presumably deterred efforts to identify such complexes and to use them in biotechnology applications. This bias was also supported by early efforts of the inventor and his co-workers to accomplish this goal through the use of well-established methods, including the yeast two-hybrid system (Fields and Song, 1989; Yang et al., 1995) and phage display (Burton, 1995). These approaches failed completely..." (Underlining supplied.)

Furthermore, there is nothing in the claims that preclude the use of "pincher" peptides. The fact that Kodacek recognized the problem and solved the problem is indicative of obviousness of the claimed invention.

Applicants argue that in Petrenko the phage-displayed library of peptides was panned against a single known target, not a surface composed of a multitude of targets.

In reply, applicants' argument is not commensurate in scope with the claims, as the claims do not recite a multitude of targets.

Applicants argue that modifying the methods of Gough according to that disclosed in Petrenko would fail to achieve the objectives of either reference.

In reply, obviousness does not require that the combined teachings of the references achieve the objectives of either



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reference. In considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also "inferences" which one skilled in the art would reasonably be expected to draw therefrom. In re Preda 159 USPQ 342. It is, of course, not necessary that Gough actually suggest, expressly or in so many words, the use of the known f8-1 peptide library used by applicants. All that is required to show obviousness is that appellants "made their claimed invention merely by applying knowledge clearly present in the prior art." In re Winslow, 53 CCPA 1574, 1578, 365 F.2d 1017, 1020, 152 USPQ 48, 50-51 (1966). It would be within the ordinary skill in the art to pick and choose a specific phage library e.g., F8-1 from the known library phages that have been employed in the art. A reference is therefore evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

The combined teachings of Gough of smaller fragments of antibodies that binds to Phytophthora with the teachings of Kodacek as to using a peptide with antibody-like properties using the known phage library f8-1 would have led one to the claimed invention. Each of the references discloses, albeit using different approaches, to only one objective i.e., the use of fragments of a macromolecule as peptides to determine its

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binding to a target (antigenic fungus). The art has shown that the (antigenic) fungal- binding resides in small region or peptide fragment of a large protein- binding target.

Applicants argue that claims 44 and 49 do not rely upon the mosaic pattern of phage coat expression. Emergent properties that inhere in the entire surface architecture may be useful whether Petrenko is trying to identify phage clones resistant to chloroform, but it remains unclear as how such emergent properties would benefit claims 44 and 49. The Office fails to explain how the mosaic pattern, described and used by Petrenko would provide an advantage in the identification of peptides with affinity for surface epitopes of *Phytophthora* fungi. Without such advantage there is no motivation to modify the methods of Gough.

In response, the billion-clone library of filamentous phage i.e., random peptide library taught by Petrenko would suggest to one having ordinary skill the use of mosaic pattern. A random library, like a mosaic pattern, contains billion combinations of compounds. The use of a multitude of clones to identify a particular desired clone would provide better chances of obtaining a particular clone with the desired property, not exclusively applied for clones resistant to chloroform. Rather,

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also applicable to the screening of peptides that would solve or eradicate fungi problems, if one so desired this object, as taught by Gough.

Applicants recognize that while the use of f88-4 peptide library in phage was known in the art, it was nevertheless nonobvious to use such f88-4 phage displayed peptide library to pan against surface exposed epitopes of Phytophthora species. The number of displayed peptides, the two pVIII genes and the mosaic pattern of wild-type and recombinant pVIII subunits in an f88-4 phage display peptide library provides neither suggestion nor motivation that these features would facilitate panning against the exposed surface of Phytrophthora.

In reply, one cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). While Gough does not teach the use of f8-1 (or f88-4) against the pathogen Phytophthora, Petrenko does. As stated in the specification the number of displayed peptides, the two genes and mosaic pattern of the wild type that results in billion peptide library would suffice as motivation to use the f88-4 library. Said f88-4 peptide library as used in the method of Gough would obviously result in the elimination, if not, complete eradication

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of a fungus by the peptide discovered from the mosaic(billion) or random f88-1 peptide library .

Applicants argue that claims 5 does not employ the open language such as "comprising" instead required that the random peptide is the disclosed sequence.

In reply, even with the use of the term "is", the peptide comprises additional sequences as shown by Seq. ID. 1. Thus, the 11-residue peptides of Petrenko are encompassed by the 33-residue peptide of the instant Seq. ID. 1. Furthermore, the random (NNN)7 encodes numerous different residues resulting in numerous peptides. Thus comprising more than the peptides as "is" recites. Applicants argue that Smith never suggests why the sequences of Petrenko et al should be modified.

In response, Smith discloses at page 243 that the fully degenerate codons (NNN) encode all 20 amino acids with no bias beyond what is entailed by the unequal degeneracy of the genetic code. The doped codons (NNK) of Petrenko are biased toward one particular amino acid in order to introduce random substitutions into a base peptide sequence. Thus, a library containing more peptide sequences would provide motivation to one having ordinary skill in the art. The presence of all 20 amino acid would produce more diverse peptide hence, discovery of a better peptide with better antifungal property.

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Applicants argue that Qui et al. would not motivate one to use the species of *Phytophthora* listed in claims 35, 36, and 48 in the method of Gough et al.

The elicitor-receptor-mediated hypersensitive response is a widely distributed pathogen defense mechanism known to occur across a variety of fungal, bacterial, and plant species. Qui et al. state that the elicitor polypeptide can be "derived from a wide variety of fungal and bacterial pathogens," a few examples of which include *Erwinia*, *Pseudomonas*, *Xanthomonas*, and *Phytophthora*. Just because a wide variety of fungal and bacterial pathogens can elicit a hypersensitive response in plants would not motivate one skilled in the art to conclude that the same variety of species would behave similarly for other, unrelated traits. The Qui et al. patent does not suggest that any of the numerous species capable of triggering a hypersensitive response in plants would be desirable in the methods of Gough et al. Applicants acknowledge that Qui et al. provided various species of *Phytophthora* as examples of sources of elicitor polypeptides. Nevertheless, argue that this disclosure would not motivate one skilled in the art to substitute various *Phytophthora* species into the methods of Gough et al. just as it would not motivate one skilled in the art to substitute species of *Erwinia*,

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Pseudomonas, Xanthamonasi or any other group of organisms known to elicit a hypersensitive response.

In reply, in the use of random peptide i.e., billion clones of peptide from the library, obviously different strains or traits of fungi can be bound by these peptides.

Claim 50 is obvious over the disclosure of Petrenko at page 799, Table 1.

Claim 51 is known in the prior art as disclosed in the specification at page 11, line 28 up to page 12, line 2.

No claim is allowed.

#### **Conclusion**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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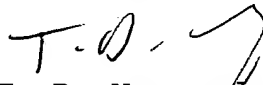
however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
T. D. Wessendorf  
Primary Examiner  
Art Unit 1639

Tdw  
July 21, 2005